

# Cost–Utility Analysis of a Medication Adherence Management Service Alongside a Cluster Randomized Control Trial in Community Pharmacy

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**Background:** It is necessary to determine the cost utility of adherence interventions in chronic diseases due to humanistic and economic burden of non-adherence.

**Purpose:** To evaluate, alongside a cluster-randomized controlled trial, the cost-utility of a pharmacist-led medication adherence management service (MAMS) compared with usual care in community pharmacies.

**Materials and Methods:** The trial was conducted over six months. Patients with treatments for hypertension, asthma or chronic obstructive pulmonary disease (COPD) were included. Patients in the intervention group (IG) received a MAMS based on a brief complex intervention, whilst patients in the control group (CG) received usual care. The cost–utility analysis adopted a health system perspective. Costs related to medications, healthcare resources and adherence intervention were included. The effectiveness was estimated as quality-adjusted life years (QALYs), using a multiple imputation missing data model. The incremental cost–utility ratio (ICUR) was calculated on the total sample of patients.

**Results:** A total of 1186 patients were enrolled (IG: 633; CG: 553). The total intervention cost was estimated to be €27.33 ± 0.43 per patient for six months. There was no statistically significant difference in total cost of medications and healthcare resources per patient between IG and CG. The values of EQ-5D-5L at 6 months were significantly higher in the IG [IG: 0.881 ± 0.005 vs CG: 0.833 ± 0.006; p = 0.000]. In the base case, the service was more expensive and more effective than usual care, resulting in an ICUR of €1,494.82/QALY. In the complete case, the service resulted in an ICUR of €2,086.30/QALY, positioned between the north-east and south-east quadrants of the cost–utility plane. Using a threshold value of €20,000/QALY gained, there is a 99% probability that the intervention is cost-effective.

**Conclusion:** The medication adherence management service resulted in an improvement in the quality of life of the population with chronic disease, with similar costs compared to usual care. The service is cost-effective.

**Keywords:** chronic disease, medication adherence, health-related quality of life, cost–utility analysis, community pharmacy services, pharmacoeconomics

## Introduction

Multi-morbidity in an aging population requires treatment with complex medication regimens leading to polypharmacy.<sup>1</sup> Medications are one of the most frequently used and effective therapeutic tools to treat diseases. Patients' adherence to medication, a complex and multifactorial concept, is a key factor to achieve optimal benefits.

From the perspective of the patient and the healthcare system, non-adherence is a pressing worldwide health problem. The World Health Organization reported in

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2003 that approximately half of patients with chronic treatments are not adherent.<sup>2</sup> Generally, it is estimated that 4% of patients do not initiate treatment, 30% are not adherent after 100 days, and 40% discontinue medications after one year.<sup>3</sup> Lack of medication adherence may lead to poor health outcomes and higher healthcare cost, due to additional physician visits, emergency care, hospitalizations and premature deaths.<sup>4,5</sup> A systematic review identified the cost of non-adherence for different diseases, with values ranging from \$949 to \$44,190 per patient per year (values adjusted to 2015).<sup>6</sup> Patients with chronic conditions, such as hypertension, asthma and chronic obstructive pulmonary disease (COPD), are particularly vulnerable to non-adherence behaviors, with estimated rates of 50% in patients suffering hypertension,<sup>7</sup> 50–60% in asthma,<sup>8</sup> and 70% in COPD.<sup>9</sup> An inadequate management of these diseases may lead to an increased use of healthcare resources, with higher costs associated with CV events attributable to hypertension,<sup>10,11</sup> poor asthma control<sup>12,13</sup> and COPD complications.<sup>13,14</sup>

Multi-component interventions<sup>15,16</sup> have been proposed to improve adherence. A systematic review summarizing the evidence on the cost-effectiveness of adherence-enhancing interventions found that, although most interventions were cost-effective or cost-saving, variation existed with intervention types.<sup>17</sup> In 2020, a Cochrane review concluded that well-designed randomized controlled trials were needed to investigate the effects of interventions for improving medication-taking ability and medication adherence in older adults who were prescribed multiple medications.<sup>18</sup> At an international level, there is extensive evidence supporting the role of pharmacists in adherence management<sup>19–29</sup> and several programs have eventuated from research. These adherence programs, implemented in several countries, vary in approach and population. For example, the Interdisciplinary Medication Adherence Program in Switzerland,<sup>30</sup> the Cardiovascular medication non-Adherence Tailored Intervention (CATI)<sup>31,32</sup> and the Medication Monitoring and Optimization (MeMO) in the Netherlands,<sup>33,34</sup> the Italian medicines use review (I-MUR) for asthma patients,<sup>35</sup> or the New Medicine Service (NMS)<sup>36–38</sup> and the Pharmacy Care Plan (PCP)<sup>39</sup> in England. However, the existing literature on economic evaluations is limited and with none being found in the Spanish community pharmacy setting.

In Spain, adherence management is identified as a national priority and has been included in a portfolio of Professional Pharmacy Services.<sup>40</sup> A randomized controlled trial in 2017–2018, AdherenciaMED,<sup>41</sup> evaluated

in community pharmacy the impact of a novel Medication Adherence Management Service. The service was delivered by community pharmacists trained in a multicomponent intervention based on behavior change models and supported for a practice change facilitator. Patients were followed for six months. Effectiveness at improving medication adherence and clinical outcomes had been reported.<sup>42</sup> The objective of this study was to evaluate the cost-utility of the pharmacist-led Medication Adherence Management Service (MAMS) compared with usual care, in patients with treatment for chronic conditions (hypertension, asthma or COPD). This paper reports on the total sample of patients.

## Materials and Methods

The study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for economic evaluations<sup>43</sup> ([Supplementary Information](#)).

## Economic Evaluation Description

A cost–utility analysis from a healthcare system perspective was undertaken with the objective of evaluating the cost-effectiveness of the MAMS performed by the intervention group (IG) compared to usual care in the control group (CG). All costs were measured in euros (€) updated to 2018<sup>44</sup> and effectiveness was estimated in quality-adjusted life years (QALYs). No discount rate was applied for costs as the study's temporal horizon was less than one year ([Table 1](#)).

## Study Design and Characteristics

The AdherenciaMED study<sup>41</sup> was designed as a cluster randomized controlled trial (cRCT), in which community pharmacies were the unit of randomization. It was conducted in six Spanish provinces from October 2017 to April 2018. The target population were patients with pharmacological treatment for one of the three chronic conditions, hypertension, asthma or COPD. All the patients were provided a patient information sheet and signed an informed consent before inclusion. Patients attended six face-to-face monthly visits in the pharmacy's counselling area. More details of study design and characteristics of this cRCT are described in a previous article.<sup>42</sup>

## Intervention Group: Medication Adherence Management Service (MAMS)

Patients in the IG received a community pharmacist-led Medication Adherence Management Service (MAMS, the

**Table 1** Components of the Economic Evaluation of the Medication Adherence Management Service

Components	Cost–Utility Analysis
Intervention	Medication Adherence Management Service (Intervention group, IG)
Comparator	Usual Care (Control group, CG)
Outcomes	Medication prescribed cost Healthcare resources cost Intervention cost Quality-adjusted life years (QALYs)
Perspective	National Health System
Time horizon	6 months
Software	Microsoft Excel STATA 15

**Abbreviations:** CG, control group; IG, intervention group; QALY, quality-adjusted life years.

Service), a tailored service to identify and address adherence or non-adherence, with the aim of improving, maintaining or reinforcing medication adherence. The service consisted of a brief complex intervention based on a combination of multicomponent strategies (behavioral change models, educational, technical) which was personalized according to the characteristics and needs of each patient. The intervention was delivered following a six-step protocol in monthly face-to-face consultations (Figure 1). All data were recorded by the pharmacist in an intervention electronic Data Collection Platform (eDCP), which guided the consultation. The pharmacist's fidelity to the intervention protocol was monitored by a practice change facilitator (PCF)<sup>45–47</sup> during their support visits. Full details of the intervention can be found in a published article.<sup>42</sup>

### Control Group: Usual Care

Patients attending CG community pharmacies received usual care and completed a total of six visits, in which the pharmacist registered in the control eDCP for control pharmacies the sociodemographic data and other variables defined for this group of patients.

### Ethics

The study was approved by the Research Ethics Committee of Granada and the Ethics Committee of University of Granada (358/CEIH/2017). The trial registration number on ANZCTR was ACTRN12618000410257.

### Costs

The subcomponents of cost included in the analysis were:

### Prescribed Medication Cost

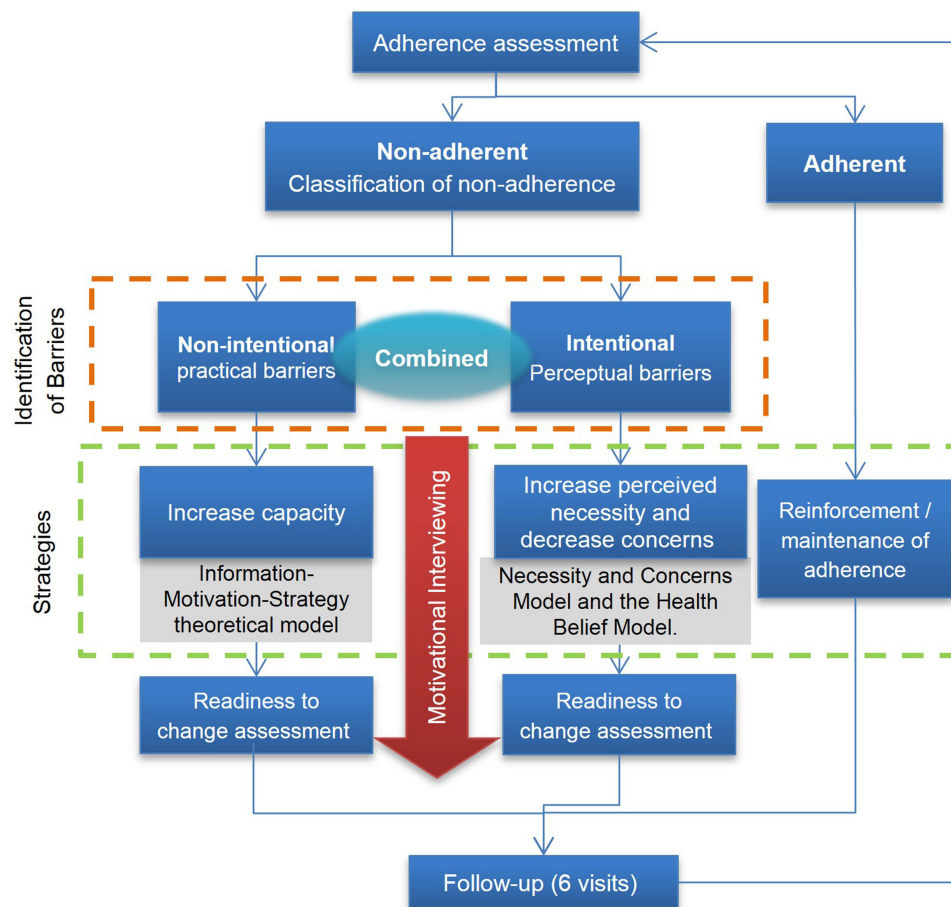
Medication prescribed was recorded by the pharmacist for both IG and CG from electronic records and the patient's self-report. Only the prescribed medication related to the study diseases were considered in the analysis. These were identified using the Anatomical Therapeutic Chemical classification system (ATC groups C02, C03, C07, C08, C09, R03).<sup>48</sup>

Medication cost was calculated using the official list of drug prices in April 2018,<sup>49</sup> taking into account the contribution of the national health system and excluding patient contributions. At baseline, the 1-month medication cost was collected, while at the end of the study, the sum of the monthly costs during the six months of follow-up was calculated.

### Healthcare Resources Cost

Data related to visits to health professionals (primary care physician, specialist physician, emergencies and hospital admissions) in the previous six months were self-reported by patients of both IG and CG. This information was collected at the baseline and at the end of the six-month follow-up.

The cost of the visits to primary care physicians, specialist physicians and emergency department were calculated using prices from each of the autonomous community [comunidad autónoma<sup>50</sup>] public health systems,<sup>51–54</sup> as prices per resource varied between different provinces. The hospital admissions cost was calculated using cost from the public system for diagnosis-related groups.<sup>55</sup>



**Figure 1** Medication Adherence Management Service intervention overview.

### Intervention Cost

Cost related to the provision of the service was considered as the time employed by the pharmacist in the activities related to the MAMS. The IG pharmacists recorded the time employed in each visit with the patients, which including time taken for the patient's interview time and data collection. The mean time per patient for the six months for each pharmacist was calculated. Using the salary in the Spanish community pharmacy agreement,<sup>56</sup> the estimated labor rate used was €0.239/min.

The pharmacy cost (investment and maintenance), training and facilitation to support the service were included in the IG arm. Firstly, the costs of the resources required to deliver the MAMS in the community pharmacies and maintenance costs over the time were included. This information was obtained from a previously published Spanish project, related to the cost of implementation of a pharmaceutical service.<sup>57</sup> The investment cost included the patient counselling area, equipment and bibliographic resources. Maintenance cost included rent for

the counselling area, utilities, equipment materials and subscriptions. General expenses and marketing were also included. These data were adjusted by the length of this study. Secondly, training cost for each pharmacist in IG was calculated by multiplying the estimated cost of labor rate of a provider pharmacist by total training time. And thirdly, the cost of the pharmacist's time spent during the visits with the PCF over six months was assessed. The cost of support visits to the pharmacy by PCF were calculated using the duration of visits and the estimated cost of labor rate.

The total number of potential patients who could benefit from the adherence service was estimated, based on the population per pharmacy ratio, the prevalence of study diseases in Spain and the estimated prevalence of non-adherence. It resulted in a potential number of 375 patients per pharmacy for 6 months. Using the total time employed by a provider pharmacist and the estimated potential number of 375 patients, the mean cost "per patient" was estimated for pharmacy, training and facilitation.

## Utility from the Health-Related Quality of Life (HR-QoL)

The HRQoL was measured with the Spanish version of EuroQol-5D-5L (EQ-5D-5L),<sup>58</sup> which was completed by patients of IG and CG at baseline, three and six months. Utility was estimated using the published Spanish tariff.<sup>59</sup> QALYs were calculated as the area under the curve.<sup>60</sup>

For missing data for the EQ-5D-5L data at three and six months, a multiple imputation with chained equations was used in order to allocate data at the different times of the study (baseline, 3 and 6 months). The multiple imputation missing data model included as predictive variables EQ-5D-5L indices at baseline and follow-up, province and study disease. Firstly, the missing data were imputed under the missing at random (MAR) assumption, the main analysis (base case). Secondly, completed case analysis was performed corresponding to a scenario where patients who completed all follow-ups can be considered representative of all the sample who initially agreed to participate, assuming data are missing completely at random (MCAR). The utilities shown in both cases have been adjusted for sex, province and disease. A simple pattern mixture model was implemented, following the approach recommended by Faria et al.<sup>61</sup>

## Cost–Utility Analysis

The results of cost–utility analysis were presented as the Incremental Cost–Utility Ratio (ICUR). Incremental cost and QALYs were calculated using bivariate regression. QALYs were adjusted for baseline EQ-5D-5L to account for differences between groups at baseline. Costs were adjusted for baseline cost, gender, province and study disease. Coefficients were combined across the multiple imputed datasets using Rubin's rules.<sup>61</sup> The probability that the intervention was cost-effective was calculated assuming the data were bivariate normal distributed.<sup>62</sup> In order to analyze the uncertainty of the ICUR, a probabilistic analysis was performed with 1000 bootstrap replications. The result was expressed in a cost-effectiveness plane and an acceptability curve. A cost-effectiveness threshold, suggested for the Spanish population, of €20,000/QALY was included.<sup>63</sup>

To assess the robustness of the results, analyses of different scenarios were performed, alongside the missing data models previously described. The first model (base case) uses multiple imputation assuming missing data are MAR. In the second model (complete case) all the patients

who did not return a HRQoL questionnaire were removed (assuming missing data are MCAR).

## Statistical Analysis

Descriptive statistics were performed. Continuous variables were described by using mean and standard error (SE). Categorical variables were described as counts and percentages. Comparison of continuous variables between groups was undertaken using T-Student test (two groups of community pharmacies). Comparison of categorical variables was undertaken using  $\chi^2$  tests or Fisher's exact test or Yates' chi-squared test when required. Significance was set at  $p < 0.05$ .

The data recorded in the eDCP by the pharmacists were extracted in Excel format. The analyses were performed using STATA 15.

## Results

### Participants

Ninety-eight community pharmacies and 138 pharmacists participated in the study. Initially, 1186 patients were recruited (CG: 553; IG: 633), with 148 patients lost to follow-up and 1038 patients (CG: 482; IG: 556) finishing the study.

Both study patient groups had similar characteristics at baseline, with a mean age of 64 years and 52.8% being female. The proportion of enrolled patients was higher for patients suffering from hypertension (CG: 219, 39.6%; IG: 283, 44.7%) and lower from COPD (CG: 154, 27.8%; IG: 145, 22.9%). There were no statistical differences in the mean number of medications used between IG and CG at baseline. There were differences in the use of healthcare resources with the number of visits to primary care physicians, specialist physicians and hospital admissions, being significantly higher in the CG (Table 2).

### Costs

#### Prescribed Medication and Healthcare Resources Cost

There were no baseline differences in the medication and healthcare resources related costs between IG and CG [IG: 72.85  $\pm$  32.06; CG: 124.00  $\pm$  30.06;  $p = 0.447$ ]. At the end of the study, the IG showed higher medication costs [IG: 228.35  $\pm$  11.98; CG: 209.52  $\pm$  10.22;  $p = 0.239$ ] and lower healthcare resources related costs; however, these differences were not statistically significant (Table 3).

**Table 2** Characteristics of Participants at Baseline (N = 1186)

	Intervention Group (n = 633)	Control Group (n = 553)	p value
Age; mean ± SE	64.0 ± 15.6	64.0 ± 15.4	1.000 <sup>a</sup>
Gender (female); n (%)	330 (52.1)	296 (53.5)	0.673 <sup>a</sup>
Education level; n (%)			
- No formal education	146 (23.1)	129 (23.3)	0.471 <sup>b</sup>
- Primary education	258 (40.8)	201 (36.3)	
- Secondary education	151 (23.9)	125 (22.6)	
- Higher non-university education	9 (1.4)	13 (2.4)	
- University education	69 (10.9)	85 (15.4)	
Employment situation; n (%)			
- Student	38 (6.0)	32 (5.8)	0.685 <sup>b</sup>
- Unemployed	62 (9.8)	51 (9.2)	
- Active worker	138 (21.8)	137 (24.8)	
- Sick leave	21 (3.3)	13 (2.4)	
- Retired	374 (59.1)	320 (57.9)	
Medications; mean ± SE			
- Total medications	5.68 ± 3.33	5.71 ± 3.49	0.901 <sup>a</sup>
- Medications for the study disease	1.82 ± 0.93	1.75 ± 0.87	0.196 <sup>a</sup>
Healthcare resources; n (%)			
- Primary care physician visits	135 (21.3)	146 (26.4)	0.040 <sup>a</sup>
- Specialist physician visits	37 (5.8)	49 (8.9)	0.046 <sup>a</sup>
- Emergency department visits	16 (2.5)	14 (2.5)	0.997 <sup>a</sup>
- Hospital admissions	4 (0.6)	12 (2.1)	0.020 <sup>a</sup>
Health Related Life Quality; mean ± SE			
- Utility score	0.82 ± 0.006	0.80 ± 0.008	0.046 <sup>a</sup>
- VAS score	68.54 ± 0.70	67.90 ± 0.81	0.540 <sup>a</sup>

Notes: Statistical tests: <sup>a</sup>t-test; <sup>b</sup>Fisher's exact test.

Abbreviations: SE, standard error; VAS, visual analog scale.

### Intervention Cost

The mean time employed by the pharmacist per patient for the provision of MAMS in the IG was 116.28 ± 42.13 minutes during the 6 months of study (19.38 min per patient per month). This involved a cost of €24.92 ± 0.43 per patient for the total six months.

Pharmacy costs based on a Spanish publication were reported to be €2,138.27 for the initial investment amortized over 5 years and €783.66 for annual maintenance.<sup>57</sup> After adjusting this data to the study period and assigning the cost to each potential patient, it resulted in €0.57 as an initial investment and €1.04 for maintenance per patient for 6 months.

There were 74 pharmacists assigned to the IG. Each pharmacist received initially a 2-day, 10-hour training. Based on the estimated cost of the pharmacist's time and after assigning the

cost to each potential patient, the cost of initial training resulted in €0.38 per patient.

Finally, the time spent during the visits of the practice change facilitator to the participant pharmacies was a mean of 11 hours per pharmacy. Based on the estimated cost of the pharmacist's time and assigning the cost to each potential patient, it resulted in €0.42 per patient for the total six months.

At the end of the study, the total cost associated with the MAMS was €27.33 per patient for six months (Table 3).

### Utility from the Health-Related Quality of Life (HR-QoL)

Two alternative analyses, using the data obtained through the EQ-5D-5L scores at three study points (baseline, 3 and

**Table 3** Medication, Healthcare Resources and Intervention Cost [€] per Patient, Baseline and in Six Months Follow-Up [Mean (SE)] (N = 1186)

	Intervention Group (n = 633)	Control Group (n = 553)	P value
● Baseline Cost (previous 6 months, except*)			
Prescribed medication (*previous month)	35.46 (1.86)	33.55 (1.63)	0.447
Primary care physician visit	13.36 (1.23)	16.57 (1.25)	0.069
Specialist physician visit	6.09 (1.03)	9.27 (1.37)	0.062
Emergency department	7.33 (1.99)	6.42 (1.82)	0.739
Hospital admissions	46.06 (31.95)	91.28 (29.52)	0.300
Total baseline cost	72.85 (32.06)	124.00 (30.06)	0.447
● Medication and healthcare resources cost (sum of 6 months follow-up)			
Prescribed medication	228.35 (11.98)	209.52 (10.22)	0.239
Primary care physician visit	19.99 (2.23)	23.51 (2.39)	0.283
Specialist physicians visit	6.50 (1.97)	6.57 (1.40)	0.978
Emergency department	6.69 (1.93)	12.01 (2.84)	0.114
Hospital admissions	42.07 (17.96)	64.85 (21.02)	0.407
Total cost in six months follow-up unadjusted	321.80 (21.24)	323.79 (24.07)	0.239
● Intervention cost (6 months follow-up)			
Time of providing service	24.92 (0.43)	–	
Initial investment in pharmacy	0.57	–	
Annual maintenance of service	1.04	–	
Initial training of pharmacist	0.38	–	
Visits of practice change facilitator to pharmacy	0.42	–	
Total intervention cost	27.33 (0.43)	–	

**Notes:** \*It should be noted that the cost of prescribed medication only corresponds to one month in the baseline, while at the end of the study the sum of cost of six months were included. Statistical tests: t-test.

6 months), were considered, which differed in the way missing data was treated (Table 4).

There were no statistical differences at baseline in mean EQ-5D-5L scores from both groups [IG:  $0.824 \pm 0.008$ ; CG:  $0.811 \pm 0.008$ ;  $p = 0.177$ ]. During the follow-up, patients in both groups perceived an improvement in their health-related quality of life, however the increase was greater in the IG [difference intragroup between baseline and month 6: IG: 0.06 vs CG: 0.03]. In the intergroup comparison, statistically significant differences were observed after the third month of the study with these remaining to the end of the study ( $p = 0.000$ ).

### Cost–Utility Analysis

Two models were considered in the cost–utility analysis (Table 5). In the first model (base case), the total mean cost was higher for the IG compared to the CG [IG: €371.93; CG: €355.04], while the mean incremental QALY between both groups was 0.011, resulting in an ICUR of €1,494.82/

QALY. In the second model (complete case), the estimated ICUR was higher than in the base case (€2,086.30/QALY) because of a higher cost difference of €21.68 and a QALY difference of 0.010 between both groups CG and IG.

The graphical representation of the complete case model, based on 1000 bootstrapped replications, showed that in the cost-effectiveness plane most of the simulations were distributed in the upper-right quadrant and the lower-right quadrant, where the most expensive and most effective health technologies are found (Figure 2).

The acceptability curve shows that, using a threshold value of €20,000 for each QALY gained, there is a 99% probability that the intervention is cost-effective for the sample in the two models (with multiple imputation and complete cases) (Figure 3).

### Discussion

This study measured the value of a community pharmacy intervention as a key element of the management

**Table 4** The EUROQOL-5D-5L Scores Adjusted of the Medication Adherence Management Service. Intervention and Control Groups [MEAN (SE)]

Alternatives	Group	Number with Missing Baseline Data	EQ-5D-5L Baseline	Number with Missing Data at 3 Months	EQ-5D-5L at 3 Months	Number with Missing Data at 6 Months	EQ-5D-5L at 6 Months
Without multiple imputation	Control	7	0.811 (0.008)	70	0.830 (0.005)	78	0.840 (0.006)
	Intervention P value	8	0.824 (0.008) 0.177	90	0.865 (0.005) 0.003	91	0.884 (0.005) 0.000
With multiple imputation (base case)	Control	0	0.804 (0.008)	0	0.822 (0.005)	0	0.833 (0.006)
	Intervention P value	0	0.825 (0.007) 0.051	0	0.863 (0.005) 0.002	0	0.881 (0.005) 0.000

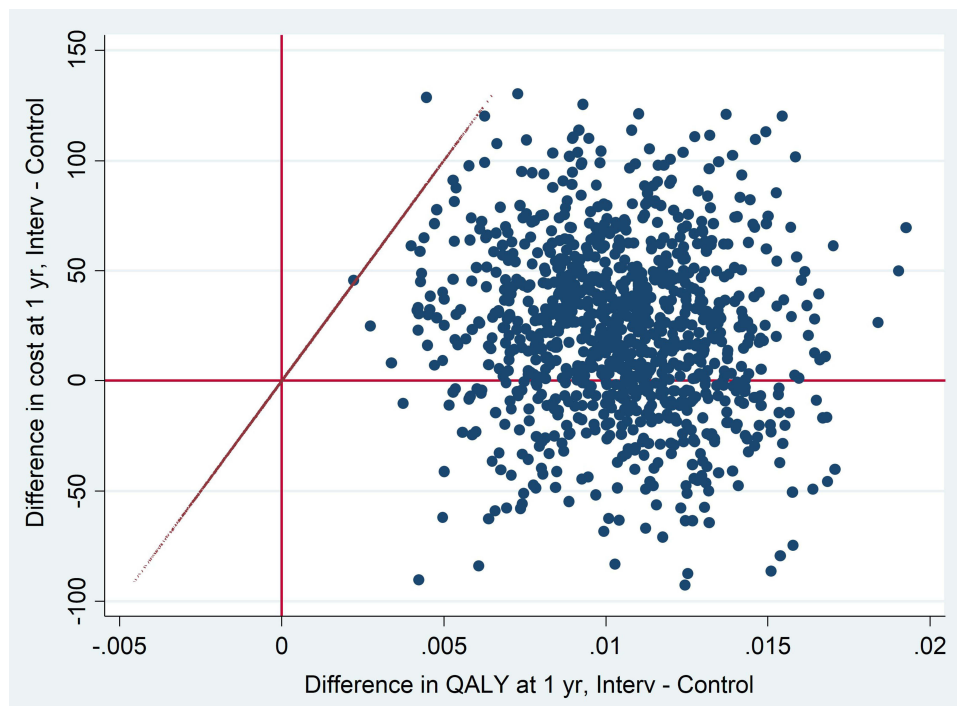
Note: Statistical tests: t-test.

**Table 5** Results of Cost-Utility Analysis and Sensitivity Analysis

	Total Cost IG	Total Cost CG	Cost Difference	QALY IG	QALY CG	QALY Difference	ICUR (€/QALY)
<b>All sample</b>							
<b>Multiple imputation (Base case)</b>	371.93	355.04	16.89	0.421	0.410	0.011	1494.82
<b>Complete case</b>	404.32	382.64	21.68	0.424	0.413	0.010	2086.30

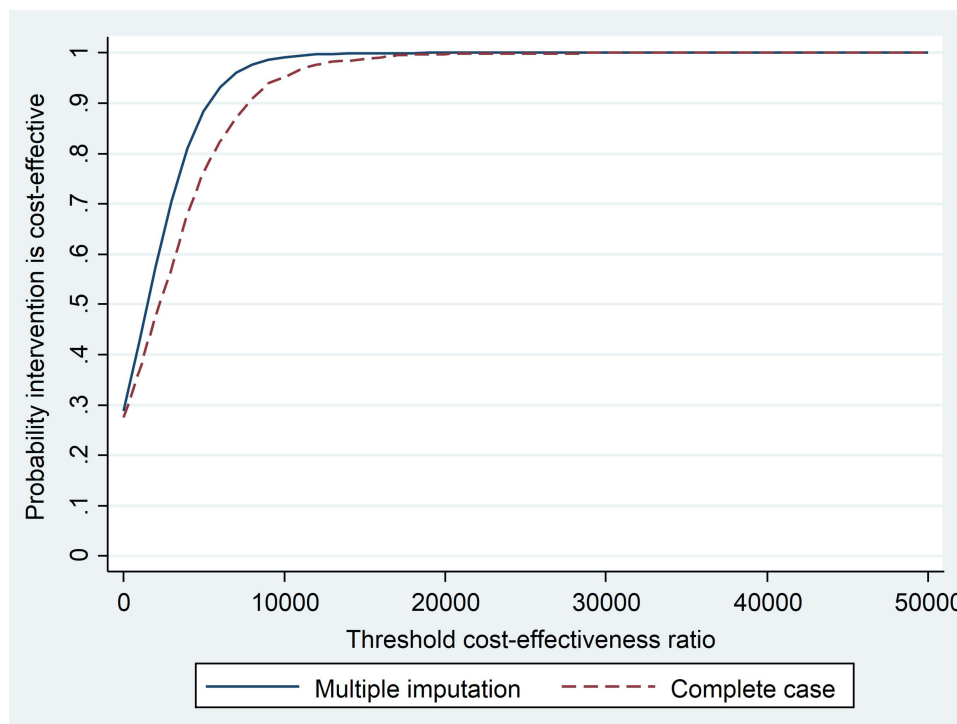
Abbreviations: CG, control group; ICUR, incremental cost-utility ratio; IG, intervention group; QALY, quality-adjusted life years.





**Figure 2** Cost-effectiveness plane for 1000 bootstrapped (complete case).

**Abbreviations:** Interv, intervention group; Control, control group; QALY, quality-adjusted life years; Yr, year.



**Figure 3** Cost-effectiveness acceptability curve for Medication Adherence Management Service.

of adherence for patients with chronic diseases, suggesting its value within primary care and the national health system.<sup>64–67</sup> The present study adds to the

evidence on economic evaluations of adherence programs in pharmacy, and fills the gap for Spanish community pharmacy.

The results of the study provided evidence that the pharmacist-led Medication Adherence Management Service significantly improved the quality of life of the population with chronic disease with a non-significant difference in costs between intervention and control groups. This study reported an analysis of costs and described those related to the components of intervention cost.

An increase, although not significant, in the medication-related cost in the intervention group compared with the control group after 6 months follow-up was found. This may be indicative of the success of the service, since the intervention facilitates the process of using medications, and encouraging the patient to take in a correct manner their medication. These findings are supported by van Boven in two studies for patients with COPD,<sup>34,68</sup> who reported an increase in medication costs associated with a greater adherence after the pharmaceutical intervention, while other studies the opposite effect was found.<sup>32,69,70</sup> For example, Khmour et al<sup>69</sup> reported that the costs of oral steroid and antibiotic courses were reduced in the intervention group in an intervention directed to increase adherence due to the decrease in exacerbations.

No significant difference was found in the cost of healthcare resources, such as self-reported visits to the primary care physician, specialist physician, emergency visits and hospital admissions. A small non-significant reduction was observed in all these variables in the intervention group. Other authors<sup>34,37,69,71</sup> have found similar results, although the components used to estimate these costs do vary between studies. Similarly in other studies,<sup>34,68–70</sup> the greatest reduction in costs was mainly associated with the decrease in hospital resources. These results however contrast with those described in two other programs,<sup>32,39</sup> which reported a non-significant increase in costs associated with the use of healthcare resources after the intervention.

The MAMS was shown to deliver clinical outcomes<sup>42</sup> with low additional costs of intervention. The global cost of providing the service per patient for six months was estimated around €27.5 (€4.55 per patient per month). In the literature reviewed, the intervention cost varies greatly between studies, due to the differences in the intervention schedule (number and type of consultations, training and materials provided, participating agents, duration of the program, etc.), the different methods and units for calculation and country. The intervention cost of the service

estimated used in our study is in the lower range between €25 - €100, compared to other programs.<sup>32,34,35,37,68</sup> Other studies have obtained higher intervention costs, due to more complex and longer interventions<sup>39</sup> or by setting a fixed fee of £51.50 for the pharmacist irrespective of the time involved.<sup>70</sup> Therefore, even though our program opted for an intensive intervention (that is, monthly face-to-face interviews) in order to establish and monitor changes in adherence behavior in patients, it has resulted in an intervention cost which is lower than that described in other studies.

The pharmacist's time costs constituted the highest proportion of costs, 91.2%, with 8.8% spent on costs related to the structure of the pharmacy, initial training and support by the practice change facilitators. As in many health services in primary care, the major investment should be directed to staff time. On average, the pharmacist devoted approximately 20 minutes per patient per monthly visit to service delivery, similar or a bit lower compared to the mean consultation times found in other studies, of 38 min<sup>68</sup> or a mean of 26 min for the initial interview and 14 min for the follow-up interview.<sup>34</sup> Brief complex interventions,<sup>72</sup> due to their brevity, may facilitate pharmacists to incorporate an adherence service as part of their existing workflows.

In real-world practice, this intervention time and therefore the major cost, for service delivery would be expected to diminish with the accumulated experience and the repetitive practice of the intervention. MAMS is a service that, due to its methodological characteristics and the nature of interventions, based on behavior change models, follows a learning curve, that is, the more times it is practiced by the pharmacist, the better the provision of the MAMS may work. Learning curves are specifically studied in healthcare education and professions where resources are limited.<sup>73–76</sup> Applied to our intervention, it means that to lower the cost of the new service, it should increase experience and practice of pharmacists, obtaining better effects after a repetition practice to complete a learning curve. Tersalvi et al<sup>77</sup> reported similar effects. In addition, a learning synergy may occur in pharmacists who are already providing other different but related services in their pharmacy.<sup>78</sup>

Despite the costs associated with the use of medication and healthcare resources not differing significantly between study groups, MAMS had a significant positive effect on health-related quality of life of patients. During the study, in the intra-group comparison, the HR-QOL

increased in both groups of patients. In the case of the control group, it may be due to the increase contact between pharmacist and patient (Hawthorne effect). However, patients in the intervention group experienced almost double the increase of the control group by the end of the study. This is higher than that found in other studies after 12 months of intervention.<sup>39,69</sup> In the intergroup comparison, a significant difference was observed after the third month. There was also a tendency to increase as the study progressed, similarly to that reported by other authors,<sup>35</sup> although this effect did not become significantly different until the sixth month. MAMS seems to add to well-being and perceived health of the population and that could be due not only to the impact of adherence but to the complexity and components of the pharmacist–patient interaction that used different models of behavior change.

In the two cost-utility sub-analyses performed, the incremental cost-utility ratio obtained showed that MAMS would be located between the north-east and south-east quadrants of the cost-utility plane. It is interesting that the literature reports conflicting results of the economic impact of adherence interventions with some studies<sup>35,38,68,69</sup> reporting a dominant ICUR and others<sup>39</sup> which reported an ICUR higher than in our study, although this particular program included a more complex intervention on the management of medications. These differences are difficult to interpret but could be due to the use of different interventions, research design and methodologies used.

Finally, in this study, considering a cost-effectiveness threshold in Spain of €20,000/QALY, the probability of MAMS being cost-effective was 99%. Similar results have been obtained in other programs, with values of 89%,<sup>38</sup> 95%<sup>69</sup> and 97%<sup>39</sup> of probability of being cost-effective, while the economic evaluation of the CATI program<sup>32</sup> obtained a higher ICUR and a 0.36 probability of being cost-effective with a willingness to pay of €20,000/QALY.

Although not evaluated in this study, the longer term improved clinical control and management, with the resultant economic benefits, are to be expected. However, since the evidence suggests that adherence is a dynamic process and is subject to change these benefits would be dependent on the continued reinforcement of adherence. Over time, an increased ability in efficacy and efficiency of the pharmacists to deliver the intervention would also be expected, which in turn may have a greater impact on adherence rates with a potential to reduce the time to deliver the intervention which was a critical cost in the cost-effectiveness analysis.

## Limitations and Strengths

A health system perspective was chosen since the main direct healthcare costs, such as medication, visits to physicians and hospitalizations could be robustly collected. However, to use a societal perspective would have been challenging to include with our research design and thus is a limitation. Also, data related to treatment dosages and utilization of healthcare resources were obtained from the patient's self-report, although this methodology is used in other studies.<sup>34</sup> The length of the study may not have allowed the effects of adherence on other variables such as the use of medications or use of healthcare resources to be observed. In contrast, the methodological characteristics and human resources allowed to recruit a large sample of patients. Additionally, the professional skills of the pharmacists who participated and the essential role of the practice change facilitator has been decisive to rigorously measure the fidelity of the intervention.

## Conclusion

The Medication Adherence Management Service, according to the cost-utility analysis performed, was shown to be a cost-effective service, with an incremental cost-utility ratio of €1,433.73/QALY in the base case analysis and €2,086.30/QALY in the complete case analysis, with potential positive gains in HRQoL, that was significantly increased with the pharmacist-led intervention. Longer term studies may be needed as it is suspected that the true gains from patients adhering to their medications may take longer than six to twelve months to have an impact on issues such as control of diseases, hospitalization rates and use of other healthcare resources. Similarly, costs of intervention may reduce as pharmacists gain greater experience with the service.

The study highlighted the role of the community pharmacist in addressing adherence and health behavior change in patients about medication use, without overlapping the roles and responsibilities of other healthcare professionals. Community pharmacies-led MAMS may be considered as a valuable service to be integrated in primary care.

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## Disclosure

The authors report no conflicts of interest in this work.

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